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Estimation of Connectional Brain Templates using Selective Multi-View Network Normalization

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Abstract. The brain connectome encodes different facets of the brain construct such as function and structure in a network. Noting that a brain network captures the individual signature of a particular subject, it remains a formidable challenge to extract a shared and representative brain signature across a population of brain networks, let alone *multi-view* brain networks. In this paper, we propose netNorm, a method that can meet this challenge by normalizing a population of multi-view brain networks, where each brain network represents a particular view of the brain, acquired using a neuroimaging technique. While conventional methods integrate the network views *equally* at a global scale, we propose a selective technique which unfolds the fusion process at a local scale by first selecting for each local pairwise connectivity between two anatomical regions of interest the *most representative cross-view feature vector* in the population. By combining the selected cross-view feature vectors, we then estimate a population representative tensor. Such multi-view representation captures the most shared traits across all subjects and thereby occupies a centered location compared to all views. In the final step, netNorm non-linearly fuses the frontal views of the estimated representative population

[†] Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNIAcknowledgementList.pdf

tensor into a single network depicting the final brain connectional template. We demonstrate the broad applicability of our method on four connectomic datasets and we show that netNorm (i) produces the most centered and representative *connectional brain template* (CBT) that consistently captures the *unique* and *distinctive* traits of a population of multi-view brain networks, and (ii) identifies disordered brain connections by comparing templates estimated using disordered and healthy brains, respectively, demonstrating the *discriminative power* of the estimated CBTs. This allows to rapidly and efficiently spot atypical deviations from the normal brain connectome for comparative studies, circumventing the need to use machine learning techniques for discriminative feature identification.

Keywords: *Connectional brain template, Network normalization, Network analysis and fusion, Disordered connectional brain alterations.*

1. Introduction

Neuroscientific and neuroimaging studies have relied heavily on the use of anatomical brain atlases for brain mapping, normalization and comparison across individuals and populations (Wu et al., 2015; Desikan et al., 2006; Dickie et al., 2017). However, the *connectional* aspect of the brain, captured by the wiring of its functional and structural neural connections, was overlooked with the exception of the work presented in (Rekik et al., 2017), which proposed the first work on estimating a brain network atlas using a population of unimodal brain networks using diffusive-shrinking graph technique. However, this work is only applicable single-view brain networks, i.e. each brain is represented by a single network. Recently, Dhifallah et al. introduced in (Dhifallah et al., 2018) the concept of population template for multi-view morphological networks using a cluster-based fusion technique. Despite its significant results, the performance of such method depends on the number of clusters used in the linear fusion step. Two of the main challenging obstacles for creating a connectional brain template for a population of multi-view brain networks lie essentially on the *inter-individual variability across subjects* for a given population, in addition to the multimodal aspect presented by the different views of the brain connectional construct. For instance, each view captures a particular aspect of the brain wiring offering different, yet, complementary information.

Recent technological advances in the field of medical imaging, in addition to the emerging international research initiatives, namely the ongoing 14 connectomic brain data gathering

studies for Connectome Related to Human Disease (CRHD)², have given rise to large neuroimaging datasets (Essen et al., 2016) acquired using various magnetic resonance imaging (MRI) modalities (structural T1-weighted, diffusion, and functional MRI). The wealth of such multimodal and large datasets can provide an excellent tool for mapping human function and cognition (Holmes et al., 2015; Park et al., 2013; Seidlitz et al., 2018), in addition to enabling the discovery of novel population-based connectomic brain signatures for a deeper understanding of different connectional patterns of both the healthy and disordered brain (Hinrichs et al., 2011; Zhang et al., 2011; Yuan et al., 2012; Thung et al., 2014; Tong et al., 2015; Farrell et al., 2009). Yet, the diversity and complexity of such data now present a major data-analytic challenge to the field of neuroscience (Jbabdi et al., 2015). Namely, how can we integrate the complementary information offered by the different brain network views into a unified normalized connectional reference for comparative studies and classification? Moreover, how can we reduce inter-subject variability in both healthy and disordered populations for better identification of 'pathological' alterations in brain networks as deviations from the 'standard' brain network representation as described in **Figure 1**?

Brain Connectional Normalization for Mapping and Diagnosis

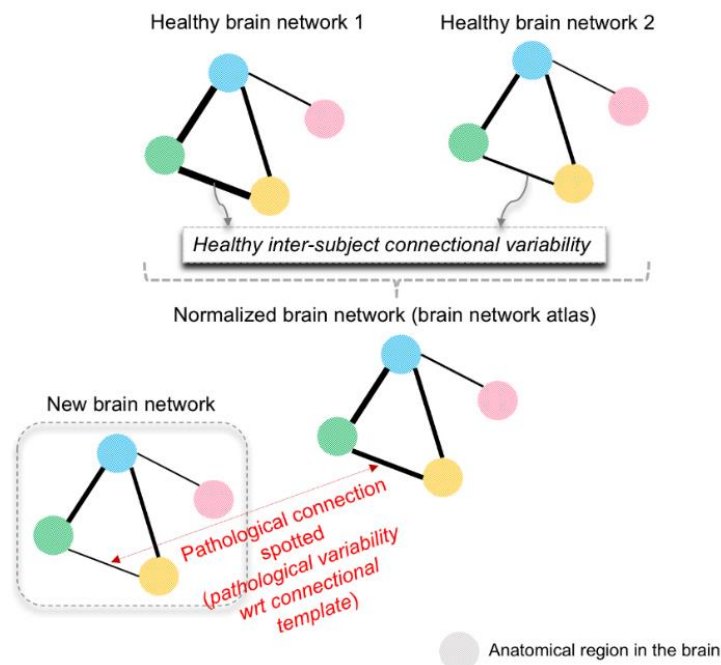


Fig. 1. Normalization of healthy brain networks for better spotting deviating pathological cases from the normalized connectional template.

² <https://www.humanconnectome.org/disease-studies>

In this paper, we propose netNorm, a novel framework that builds a connectional template for a population of multi-view brain networks. The key idea is to first create a representative tensor which is a mosaic representation capturing the most common cross-view feature vectors across subjects in a *selective manner*, then we *non-linearly* fuse the different layers of the representative tensor into the final unified connectional brain template (CBT). We refer to this network normalization method as netNorm (<https://github.com/basiraLab/netNorm3>). We demonstrate that netNorm outputs multi-view population-driven CBTs satisfying the following criteria: (i) they are well-centered and representative i.e., occupy the minimum distance to all brain views and to all subjects in a given population, and (ii) they can effectively and easily reveal discriminative brain connections that distinguish between two populations (e.g., healthy and demented brain networks) by well capturing population-specific traits and assuring robustness against inter-individual variance (Wu et al., 2011). netNorm is a simple and innovative framework that estimates multi-view brain connectional templates, thereby providing an integral representation of multi-view brain connections across subjects in a given population. More importantly, we also investigate the discriminative power of the estimated template in distinguishing between healthy and disordered brains. In other words, can we leverage the estimated connectional templates to spot disordered brain regions for disentangling different brain conditions (e.g., healthy *versus* disordered)?

2. Proposed netNorm framework

In the mid-1990s, Erich Fromm, a social psychological, introduced “the social character theory” on defining a society's psychological traits (Rickert et al., 1986). Unlike individual psychoanalysis, Fromm assumes that, at a group scale, psychological traits are no longer defined by the complete image of individual's psyche, rather it is based on the common psychological features across the group members. By analogy to Fromm's theory, if we consider that cross-view feature vectors capturing connectivity weights between pairs of ROIs across all views represent our population's traits, then a population template can be defined using the most common feature vectors across all subjects. Hence, we define a *commonality criterion* for each pair of ROIs using inter-subject feature vector distances. This criterion guides our cross-view feature vectors' selection process to construct a population representative brain tensor depicting the most common traits of our population across all subjects. Ultimately, by applying non-linear

³ The code will be released upon the acceptance of the paper

fusion, we then integrate the different views of the constructed tensor into a single connectivity network presenting the final population template.

In this section, we denote tensors by boldface Euler script letters, e.g., \mathcal{X} . Matrices are denoted by boldface capital letters, e.g., \mathbf{X} , vectors are denoted by boldface lowercase letters, e.g., \mathbf{x} , and scalars are denoted by lowercase letters, e.g., x . For easy reference, we have summarized the major mathematical notations presented in this paper in **Table 1**.

Table 1. Major mathematical notations used in this paper.

Mathematical notation	Definition
N	total number of subjects in the population
n_v	total number of brain views for each subject
n_r	total number of regions of interest in the brain
\mathcal{J}^s	subject's representative tensor $\in \mathbb{R}^{n_r \times n_r \times n_v}$
\mathbf{X}_k^s	k^{th} network view for subject $s \in \mathbb{R}^{n_r \times n_r}$
\mathbf{V}_{ij}^s	feature vector for subject s related to ROIs i and $j \in \mathbb{R}^{n_v \times 1}$
\mathbf{H}_{ij}	high-order graph (graph of a graph) for pair of ROIs i and $j \in \mathbb{R}^{N \times N}$
$\tilde{\mathcal{J}}$	population's representative tensor $\in \mathbb{R}^{n_r \times n_r \times n_v}$
$\tilde{\mathbf{X}}_v$	v^{th} population's representative brain view $\in \mathbb{R}^{n_r \times n_r}$
\mathbf{P}_v	status matrix for view $v \in \mathbb{R}^{n_r \times n_r}$
\mathbf{S}_v	kernel matrix for view $v \in \mathbb{R}^{n_r \times n_r}$
\mathbf{A}	estimated connectional brain template (or atlas) $\in \mathbb{R}^{n_r \times n_r}$

We illustrate in **Figure 2** netNorm steps for brain connectional template estimation from multi-view connectomic data. First, for each subject in a population of interest, we build a population of multi-view brain networks by defining different morphological brain views. Then, for each pair of ROIs i and j , we define a cross-view feature vector combining their connectivity weights across all views. In the next step, we construct a high-order graph for each pair of ROIs i and j , modeling the relationship between the different subjects' feature vectors. Using the defined graph, we then define a commonality criterion guiding a feature vector selection process. We repeat the same process for all cross-view feature vectors created for each pair of ROIs in order to construct the population representative tensor. The final CBT is then obtained by applying non-linear fusion for different representative tensor views.

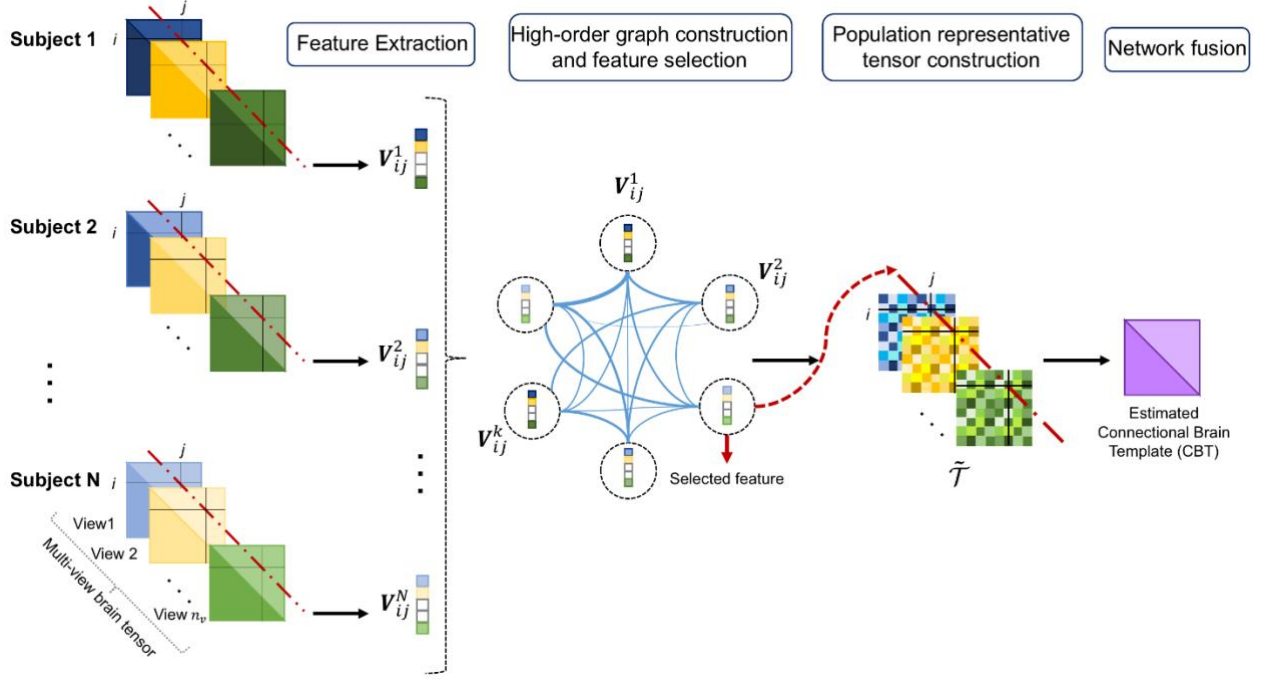


Fig. 2. Overview of netNorm pipeline for connectional brain template (CBT) estimation from multi-view brain networks. Given a population of N multi-view tensors, where each subject-specific tensor comprises a set of stacked brain network views, we first extract a feature vector V_{ij}^k for each subject k and each pair of brain regions of interest (ROIs) i and j . Each feature vector V_{ij}^k is composed of connectivity weights between ROIs i and j derived from all views. Next, for each pair of ROIs, we construct a high-order graph modeling inter-subject relationship. Each graph node embeds a feature vector V_{ij}^k for subject k in the population and the strength of an edge connecting two nodes k and k' is calculated as the Euclidian distance between V_{ij}^k and $V_{ij}^{k'}$. The node satisfying the minimum mean distance to all other nodes is then selected as a population-specific feature vector representative. By selecting the optimal population-specific feature vectors for each pair of ROIs, we construct the population representative tensor \tilde{T} . Finally, we generate brain connectional template by non-linearly fusing all tensor layers using similarity network fusion (SNF) technique.

2.1 Multi-view morphological brain network construction

The two most widely used measures of brain connectivity for mapping brain wiring in the literature are functional connectivity and structural connectivity, derived from functional magnetic resonance imaging (fMRI) and diffusion weighted imaging (DWI), respectively (Lerch et al., 2017). Yet, these imaging techniques present the limitations of time-consumption, high cost and proneness to noise (Lisowska et al., 2018). Recent works (Lisowska et al., 2018;

Mahjoub et al., 2018; Raeper et al., 2018; Soussia et al., 2018) have considered the use of morphological connectional features in order to circumvent these limitations. Brain morphology including cortical measures (e.g., cortical thickness) can be used as biomarkers for neurodevelopmental (i.e., ASD) (Wallace et al., 2010; Hardan et al., 2009) and neurodegenerative (i.e., AD) diseases (McEvoy et al., 2009; Ridgway et al., 2012). More specifically, brain morphological changes may reflect abnormal functional and structural connections (Essen et al., 1997). Inspired by these works (Lisowska et al., 2018; Mahjoub et al., 2018; Raeper et al., 2018; Soussia et al., 2018) as well as the work of (Seidlitz et al., 2018) investigating the relation between morphological similarity networks and cognition, we propose to evaluate netNorm using multi-view brain morphological networks derived from different morphological measurements relating brain regions to one another. Hence, for each subject in the population, we define a single-view morphological brain network (MBN) as a graph where nodes represent cortical regions of interest (ROIs) and edges encode the interconnections between different nodes capturing their dissimilarity in morphology using a specific cortical attribute (e.g., cortical thickness, sulcal depth). More specifically, we represent each network as a matrix \mathbf{X} in $\mathbb{R}^{n_r \times n_r}$, where n_r represents the number of ROIs. For each ROI, we first compute the average value of a cortical attribute. Next, we define each element $\mathbf{X}(i, j)$ as the absolute difference between the average cortical attributes in ROIs i and j , denoting the weight of the link between both regions of interest. Using different morphological measurements, we can generate multiple network views for each individual, where each view is represented by an $n_r \times n_r$ connectivity matrix (**Figure 3**). Given a population of N subjects where each subject s is represented by n_v brain network views, let \mathbf{X}_k^s denote the k^{th} network view (or matrix) for subject s . We can then represent each subject s by a tensor $\mathcal{T}^s \in \mathbb{R}^{n_r \times n_r \times n_v}$ where its k^{th} frontal view represents a brain connectivity matrix \mathbf{X}_k^s . Note that we set the diagonal for each matrix \mathbf{X}_k^s to zero in order to avoid self-similarity.

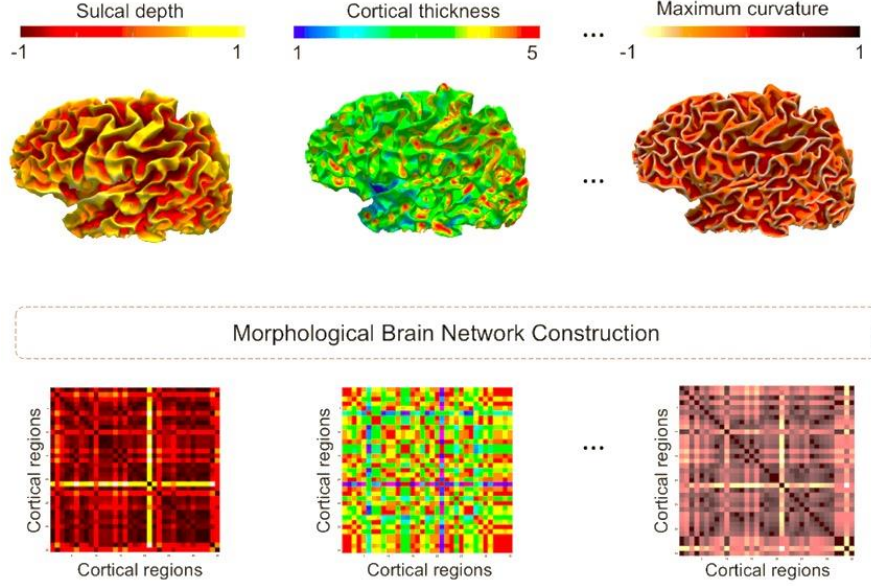


Fig. 3. Morphological brain network construction for a representative subject using different views of the cortical surface. Each view is represented by a matrix quantifying the dissimilarity between each pair of ROIs in the brain in terms of a specific morphological attribute (e.g., sulcal depth, cortical thickness).

2.2 Connectional feature extraction

For each subject s , we define a cross-view feature vector (weight vector) \mathbf{V}_{ij}^s ; $1 \leq i, j \leq n_r$ for each pair of ROIs i and j . Specifically, \mathbf{V}_{ij}^s captures the connectivity between ROIs i and j across all views. Each subject-specific feature vector is defined as follows:

$$\mathbf{V}_{ij}^s(k) = \mathcal{T}^s(i, j, k), \forall 1 \leq k \leq n_v, \quad \forall 1 \leq i, j \leq n_r$$

Considering that brain networks can be represented as symmetric matrices with null diagonal, we only use the upper triangular part, thereby decreasing the total number of cross-view feature vectors for each subject from n_r^2 to $N_f = \sum_{i=1}^{n_r-1} (n_r - i) = \frac{n_r(n_r-1)}{2}$.

2.3 High-order graph construction

In order to unravel the complex relationships between subjects in a specific population for the normalization process, we propose to build an $N \times N$ high-order graph \mathbf{H}_{ij} for each pair of ROIs i and j (i.e., for each brain connectional feature). Such a high-order representation would help reveal cross-view feature vectors' dissimilarities across subjects for a given population by computing the inter-individual distances for each pairwise feature vector. For a pair of ROIs i and j , \mathbf{H}_{ij} is composed of a set of N nodes $\{\mathbf{V}_{ij}^1, \dots, \mathbf{V}_{ij}^N\}$, each representing a subject-specific

cross-view feature vector \mathbf{V}_{ij}^s for a subject s . The edges are calculated based on the Euclidean distance between feature vectors for each pair of subjects in the population. For ROIs i and j , the edge between subjects s and s' is calculated as follows:

$$\mathbf{H}_{ij}(s, s') = \sqrt{\sum_{k=1}^{n_v} (\mathbf{V}_{ij}^s(k) - \mathbf{V}_{ij}^{s'}(k))^2}; \forall 1 \leq s, s' \leq N$$

2.4 Quantifying the centeredness of each subject for a specific pair of ROIs

For each pair of ROIs i and j , we construct an $N \times 1$ distance vector \mathbf{D}_{ij} calculated by summing \mathbf{H}_{ij} rows:

$$\mathbf{D}_{ij}(s) = \sum_{s'=1}^N \mathbf{H}_{ij}(s, s') = \sum_{s'=1}^N \sqrt{\sum_{k=1}^{n_v} (\mathbf{V}_{ij}^s(k) - \mathbf{V}_{ij}^{s'}(k))^2}$$

Where $\mathbf{D}_{ij}(s)$ is the cumulative distance from a feature vector \mathbf{V}_{ij}^s for subject s to all remaining subjects in the population, $\mathbf{V}_{ij}^{s'}, \forall 1 \leq s' \neq s \leq N$. The intuition behind this step is to define an inclusiveness (commonality) criterion for each feature type across the whole population, where the feature vector satisfying the smallest distance $\min_{1 \leq s \leq N} \mathbf{D}_{ij}(s)$ depicts the most representative and centered trait (cross-view feature vector) across all subjects.

2.5 Population-representative tensor construction

Instead of using the whole population dataset to build the final CBT, netNorm constructs a population-representative tensor $\tilde{\mathcal{T}}$ as follows:

$$\tilde{\mathcal{T}}(i, j, k) = \mathbf{V}_{ij}^{s'}(k); \forall 1 \leq k \leq n_v; \text{ where } s' = \min_{1 \leq s \leq N} \mathbf{D}_{ij}(s)$$

In essence, $\tilde{\mathcal{T}}$ is constructed using a selection process that takes into consideration 'the best' cross-view feature vectors (nearest feature to all others). The intuition behind this step is to define a multimodal brain network that captures the most shared traits of the population while

'overlooking' the peculiarities of individual subjects which is the case for network brain average that treats all subjects equally in the fusion process.

2.6 Non-linear fusion for connectional brain template estimation

Since the relationship between brain connections across views is complex and nonlinear, netNorm non-linearly merges the n_v views of the population's representative tensor $\tilde{\mathcal{T}}$ in order to obtain the final CBT. To this aim, we use similarity network fusion (SNF) introduced by Wang *et al.* in (Wang et al., 2014). SNF is a framework that integrates networks defined using different data types for a same set of samples into a single network that gathers both local and global traits of similarities between samples. This final matrix is then used for retrieval, clustering or classification.

In our case, we leverage SNF technique to generate a CBT using the n_v network views composing $\tilde{\mathcal{T}}$. The first step is to initially construct a status matrix \mathbf{P}_v for each view v carrying the whole information about ROIs' similarities and a local matrix \mathbf{S}_v that only takes into consideration the similarity to the K nearest neighbours of each ROI. This fusion technique is based on iteratively updating each individual status network \mathbf{P}_v in the population through diffusing the average global structure of other $N - 1$ networks along the individual local sparse matrix \mathbf{S}_v . \mathbf{P}_v and \mathbf{S}_v are calculated as follows:

$$\mathbf{P}_v(i, j) = \begin{cases} \frac{\tilde{\mathbf{X}}_v(i, j)}{2 \sum_{l \neq i} \tilde{\mathbf{X}}_v(i, l)}, & j \neq i \\ 1/2, & \text{if } i = j \end{cases}$$

$$\mathbf{S}_v(i, j) = \begin{cases} \frac{\tilde{\mathbf{X}}_v(i, j)}{\sum_{l \in N_i} \tilde{\mathbf{X}}_v(i, l)}, & j \in N_i \\ 0 & \text{otherwise} \end{cases}$$

Where $\tilde{\mathbf{X}}_v$ is the v^{th} frontal view of $\tilde{\mathcal{T}}$ denoting the v^{th} population's representative brain view, and N_i is the set of neighbors of ROI i . This is achieved through iteratively updating the following equation:

$$\mathbf{P}_v^t = \mathbf{S}_v \times \left(\frac{\sum_{v' \neq v} \mathbf{P}_{v'}^t}{n_v - 1} \right) \times (\mathbf{S}_v)^T$$

Where $t \in \{0, \dots, t^*\}$ denotes the diffusion iteration number and T denotes the matrix transpose operator. Finally, following t^* iterations, the target CBT is generated by averaging all updated diffused networks:

$$\mathbf{A} = \frac{1}{n_v} \sum_{k=1}^{n_v} \mathbf{P}_v^{t^*}$$

Remark on using SNF to fuse dissimilarity matrices. Originally, SNF technique (Wang et al., 2014) is used to fuse similarity networks for clustering purposes. In this remark, we mathematically demonstrate that SNF can be also applied to fuse dissimilarity data where the different connections between ROIs denote distance measures. We introduce below the different steps of SNF algorithm for data fusion as introduced in (Wang et al. 2014).

Alg.1: SNF algorithm for fusing matrices (Wang et al. 2014)

1: Inputs:

A set of m similarity matrices: $\mathbf{W}_k(i, j)$

2: Defining a status matrix for each similarity matrix \mathbf{W}_k :

for each matrix \mathbf{W}_k **do**

for each pair of ROIs i and j **do**

$$\mathbf{P}_k^0(i, j) = \begin{cases} \frac{\mathbf{W}_k(i, j)}{2 \sum_{l \neq i} \mathbf{W}_k(i, l)} , & j \neq i \\ 1/2 , & j = i \end{cases}$$

end

end

3: Defining the K nearest neighbours for each ROI x_i and for each view k :

for each matrix \mathbf{W}_k **do**

for each ROI i **do**

 Find the K nearest neighbours N_i for each ROI x_i :

N_i corresponds to the K ROIs x_l where $\mathbf{W}_k(i, l)$ is maximum (the most similar ROIs to x_i).

end

end

4: Defining a local matrix for each similarity matrix W_k :**for each matrix W_k do****for each pair of ROIs i and j do**

$$S_k(i, j) = \begin{cases} \frac{W_k(i, j)}{\sum_{l \in N_i} W_k(i, l)}, & j \in N_i \\ 0, & \text{otherwise} \end{cases}$$

end**end****5: Iteratively updating the status matrix for each view k :****for each view k do**

$$P_k^{t+1} = S_k \left(\frac{\sum_{v \neq k} P_v^t}{m-1} \right) (S_k)^T, k = 1 \dots m$$

end**6: Defining the final fused similarity matrix:**

$$P_c = \frac{\sum_{1 \leq k \leq m} P_k^t}{m}$$

Considering **Alg.1**, we note that while the different steps (1, 2, 5 and 6) are mathematically applicable to any type of data (dis/similarity), step 3 and 4 consider pairwise similarities within a network and use them as a reference for uncovering the inner structure of the input data by defining the local matrix for each view. The question that arises at this point is: “*Is this technique applicable for dissimilarity networks where the connectivity values denote distances instead of similarities?*”

The essential role of defining the local matrix S_k is to unravel the local structure of the sample matrices in terms of strong and weak connections. For similarity matrices, we aim to enhance similarities across ROIs, while for dissimilarity matrices, we aim to discover the strongest connections in terms of distances measures (dissimilarities).

According to SNF algorithm (**Alg.1**, Wang et al. 2014), the set of most similar ROIs $N_i = \{x_j\}_j$ to each ROI x_i are defined by choosing the first K regions x_j with the maximum connectivity measure $W_k(i, j)$. The intuition behind this step is to define a local matrix S_k capturing the local structure of the network. Only strong connections denoting the most similar connections remain strong while weak connections disappear. Integrating S_k into the fusion process would help enhance the strong similarity connections across networks. In case where the input networks are encoded in *dissimilarity* matrices as in our experiments, the connections between

pairs of ROIs denote the distance between them. Hence, larger values represent most dissimilar pairs of ROIs. Applying step 3 in **Alg.1**, by picking the top ROIs with the maximum connectivity values to an ROI x_i , we are enhancing the dissimilarity between pairs of ROIs across all views. The local structure of the networks would then denote the local dissimilarities across ROIs while reducing the most similar connections. Using the local matrix \mathbf{S}_k in the fusion process, strong dissimilarities will get stronger and weak dissimilarities will get weaker. For better reference, we present in **Figure 4** an example illustrating the definition of local matrices for both similarity and dissimilarity sub-networks.

In conclusion, from a mathematical perspective, the different steps of SNF algorithm are applicable to both similarity and dissimilarity networks. Therefore, SNF can be used to fuse any type of data regardless of the nature of their inner connection. \square

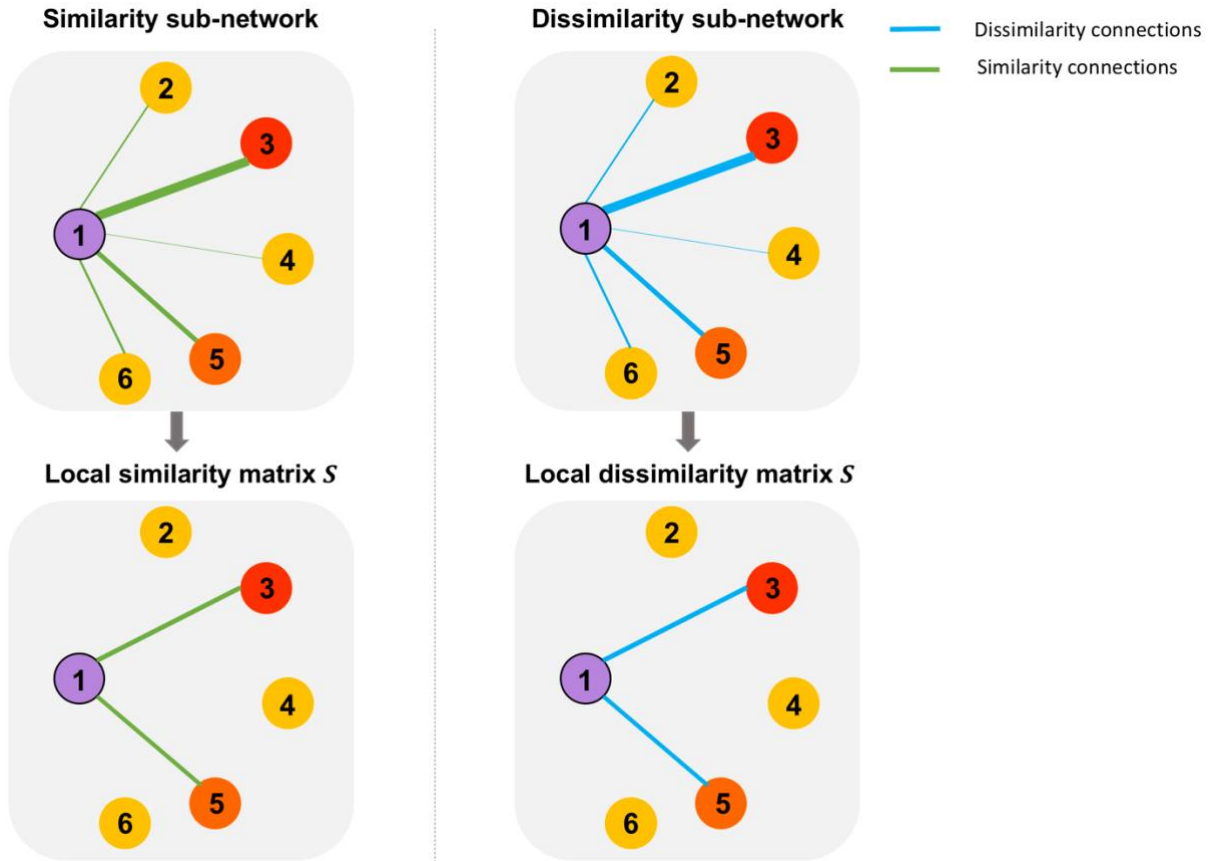


Fig. 4: Illustration of SNF local matrix derived from similarity and dissimilarity sub-networks centered at a single seed node (purple node). Strong connections in terms of similarity and dissimilarity measures are respectively transformed into similarity and dissimilarity local matrices after normalization where weak connections disappear for both. The number of neighbors K is set to 2 and the neighborhood for node 1 is defined as $N_1 = \{x_3, x_5\}$ in both sub-networks.

3. Experiments and material

3.1 Evaluation connectomic datasets

We evaluated netNorm on two datasets as detailed in **Table 2**, where each subject is represented by four morphological brain networks. The first dataset (ASD/NC dataset) is collected from the Autism Brain Imaging Data Exchange ABIDE I public dataset⁴ and consists of 341 subjects: 155 normal controls (NC) and 186 subjects with autism spectrum disorder (ASD) (Martino et al., 2014). The second dataset (LMCI/AD dataset) is collected from Alzheimer’s Disease Neuroimaging Initiative (ADNI) database GO public datasets consisting of 77 subjects: 36 subjects with Late Mild Cognitive Impairment (LMCI) and 41 subjects with Alzheimer disease (AD) (Mueller et al., 2005). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer’s disease (AD).

Table 2. Data distribution for LMCI/AD and NC/ASD datasets.

Datasets	AD/LMCI		ASD/NC	
	AD	LMCI	ASD	NC
Number of subjects	41	36	155	186
Male	23	20	140	155
Female	18	16	15	31
Mean age	75.27	72.54	16.92	16.6

We used FreeSurfer pipeline (Fischl et al., 2012) to reconstruct both right and left cortical hemispheres (RH and LH) for each subject from structural T1-weighted MRI. We parcellated each hemisphere into 35 cortical regions of interest using Desikan-Killiany atlas (Fischl et al., 2004). Finally, we generated 4 cortical morphological brain views (networks) for each hemisphere as shown in **Figure 3**: X_1 , X_2 , X_3 and X_4 denoting respectively the maximum

⁴ http://fcon_1000.projects.nitrc.org/indi/abide/

⁵ Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

principal curvature, the mean cortical thickness, the mean sulcal depth, and the average curvature.

Source code. netNorm source code is available at <https://github.com/basiralab/netNorm>.

3.2 Evaluation of connectional brain template representativeness

To evaluate the centeredness and representativeness of the estimated CBT in the original manifold where all multi-view networks are nested, we calculate the mean Frobenius distance from each view of each subject in the population to the estimated template. The mean Frobenius distance between 2 matrices \mathbf{A} and \mathbf{B} is calculated as: $d_F(A, B) = \sqrt{\sum_i \sum_j |a_{ij} - b_{ij}|^2}$. For reproducibility and generalizability, we used 5-fold cross-validation where we divided each population into 5 sub-populations. We used each sub-population to generate a connectional template and calculate its distance to all views within the subgroup. Hence, for each population (e.g., ASD), we generated 5 CBTs, with an additional one using the whole data.

For a clear representation of the results, we normalize the Frobenius distances calculated using netNorm and state-of-the-art techniques within each fold using the following formula:

$$d'_F = (d_F - \text{mean}_i) / (\text{max}_i - \text{mean}_i) + 1.5$$

Where mean_i and max_i denote respectively the average and the maximum values of the Frobenius distances calculated using the different distances for a given fold i .

To assess the statistical significance of netNorm, we validated the comparative study of the CBTs centredness using a two-tailed paired t-test across all data folds in addition to the whole data between netNorm and each of the comparative methods.

3.3 Evaluation of connectional brain template discriminability

In order to test the discriminability of the estimated CBTs, we conducted a group comparison study to identify the top brain ROIs that distinguish between two groups: (1) ASD vs. NC, and (2) LMCI vs. AD, respectively, using both left and right hemispheres. For this aim, we estimated a MV-CBT for each group, then by computing the difference between both templates (e.g., NC and ASD templates) we identified the top 15 ROIs that distinguish between both groups. Next, we computed the overlap (in %) between the top discriminative ROIs found by netNorm and a supervised machine learning method based on multiple kernel learning (MKL). Both methods are detailed bellow.

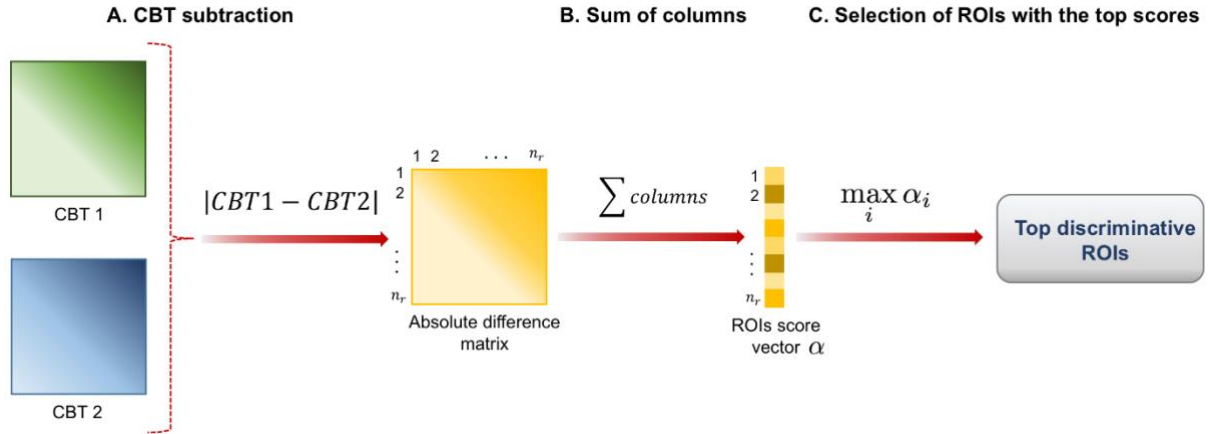


Fig. 5. Identification of the top 15 discriminative regions of interest (ROIs) using the estimated connectional brain templates (CBTs) by netNorm. (A) We compute the absolute element-wise difference between both CBTs to generate the absolute difference matrix. (B) By summing up the column elements of each row in the absolute difference matrix, we create a score vector assigning the weight for each ROI. (C) Top discriminative ROIs are then identified using the highest scores.

3.3.1 Top discriminative ROIs identification using the estimated CBTs

To assess the reproducibility of CBT produced by netNorm, we used randomized 5-fold partition to divide each population p and p' into 5 folds: p_i and p'_j , respectively, where $1 \leq i, j \leq 5$. A_i^p and $A_j^{p'}$ denote the estimated CBT for the i^{th} fold in p and the j^{th} fold in p' . We compute the mean absolute difference between the estimated templates across folds using a simple inter-template subtraction as follows:

$$D = \sum_{i,j=1}^5 |A_i^p - A_j^{p'}|$$

Where D is an $n_r \times n_r$ matrix containing absolute features' differences between fold p_i and fold p'_j in terms of connectional strength. By summing the columns of D , we obtain a score vector α where the i^{th} coefficient denotes the score α_i assigned to the i^{th} ROI representing the cumulative distance from ROI i to all other ROIs $k \neq i$. α_i is calculated as follows:

$$\alpha_i = \sum_{\substack{k=1 \\ k \neq i}}^{n_r} D(i, k)$$

The top discriminative ROIs are then identified as those with the highest scores (**Figure 5**).

3.3.2 Top discriminative ROIs identification using MKL

Multiple kernel learning (MKL) is a technique aiming to identify the most discriminative features for a target classification task that distinguishes between two classes p and p' . Given a set of labelled data, each represented by a feature vector, we train a support vector machine (SVM) classifier that learns a weight for each feature type quantifying its discriminative power in the classification task.

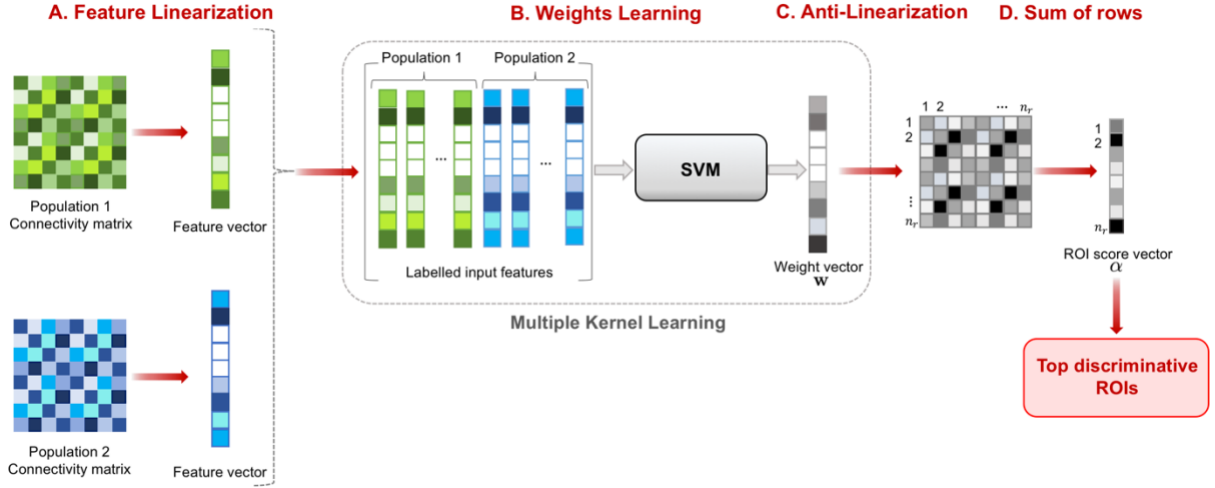


Fig. 6. Identification of the top discriminative ROIs using Multiple Kernel Learning (MKL). (A) We vectorized upper triangular part of each population matrix to generate a feature vector for each connectional network. (B) Using multiple kernel learning (MKL), we obtain a weight vector \mathbf{w} quantifying the discriminability of each brain feature (i.e., brain connectivity between two regions of interest (ROIs)). (C) We use anti-linearization to transform the weight vector into a matrix where each element represents the weight of a connectivity between two ROIs. (D) By summing up the columns of the produced matrix we get a score vector denoting the discriminability of each ROI.

For each network view, we used 5-fold randomized partitioning of data samples to divide each population p and p' into 5 subpopulations. Given the v^{th} brain view, for each combination of subpopulations p_i and p'_j , where $1 \leq i, j \leq 5$, a connectional feature vector \mathbf{F}_s^v is constructed for each subject s in both subpopulations using the vectorized upper triangular part of the connectivity matrix \mathbf{X}_s^v . We assign a label $y_s^v \in \{\pm 1\}$ for each feature vector \mathbf{F}_s^v denoting the population class. Feature vectors and their labels are then used as inputs to train an SVM classifier. Using wrapper method, a weight vector \mathbf{w}_{ij}^v is estimated to assign a weight score for each feature (connectional strength) in the classification process using view v and subpopulations p_i and p'_j . The final weight vector \mathbf{w} is then calculated by summing up the weight vectors across all views and all combinations of subpopulations:

$$\mathbf{w} = \sum_{v=1}^{n_v} \sum_{i,j=1}^5 \mathbf{w}_{ij}^v$$

Then, we assign a score value α_i to the i^{th} ROI by adding up the weights of all connections involving ROI i to other ROIs. Let $\mathbf{w}(i, j)$ denote the weight of the connectivity strength between ROIs i and j , α_i is then calculated as follows:

$$\alpha_i = \sum_{j \neq i} \mathbf{w}(i, j)$$

Finally, we select the top discriminative ROIs using the highest scores α_i , where $1 \leq i \leq n_r$ (**Figure 6**).

4. Results

For comparative evaluation, we benchmarked netNorm against SCA method introduced in (Dhifallah et al., 2018) in addition to four baseline methods, relying on either of the following two key steps or both: (1) we merge the different views at the individual level, and (2) we fuse the resulting views from step (1) at the population level into a single network representing the final CBT. Both steps are conducted using one of the following merging techniques: linear fusion (average of different views) or non-linear similarity network fusion (SNF) (Wang et al., 2014). These four include SNF-SNF (SS), Average-Average (AA), SNF-Average (SA), and Average-SNF (AS). The number of iterations used in SNF is set to $N_t = 20$ to guarantee its convergence as recommended in (Wang et al., 2014). We empirically set the number of nearest neighbors to $q = 20$.

CBT representativeness and centredness. In order to evaluate the representativeness of the proposed CBT, we computed the mean Frobenius distance between the estimated brain network and the different views in the population for baseline methods as well as the proposed framework for both hemispheres (LH: the left hemisphere and RH: the right hemisphere). **Table 3** displays the mean Frobenius distance between the estimated CBTs calculated using the whole dataset for baseline methods as well as the proposed framework. We note that our proposed CBT remarkably and consistently outperforms conventional techniques by achieving the minimum distance for all datasets using both hemispheres offering the most centered brain template for each population. **Figure 7** further plots the mean normalized distances between the estimated CBT and all views in the population for each hemisphere in our four datasets (AD, LMCI, ASD, NC) using 5-fold cross validation to evaluate the generalizability of our

results across folds and when scaling up the data (i.e., considering the whole dataset). We note that netNorm consistently outperforms comparison methods in terms of centredness when applied to all populations using both hemispheres for a p-value < 0.001 using two-tailed paired t-test. In fact, the estimated CBTs using netNorm constantly have the minimum normalized mean distance to all views across all subjects followed by SCA (Dhifallah et al., 2018), SA, AS, SS and AA techniques, respectively. We did not include the results of AA method in **Figure 7** since its distance values largely exceed the average range of other distances.

Table 3. Normalized mean Frobenius distance between the estimated connectional brain template and the different connectional brain views using all subjects in different datasets. LMCI: late mild cognitive impairment. AD: Alzheimer’s disease. NC: normal controls. ASD: autism spectrum disorder.

Datasets	ASD		NC		LMCI		AD	
	LH	RH	LH	RH	LH	RH	LH	RH
AA ($\times 10^{-2}$)	11.54	11.01	13.95	13.41	7.71	5.39	6.25	5.48
SS	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
AS	2.08	2.31	2.25	2.46	1.92	1.90	1.82	1.85
SA	0.85	0.72	0.74	0.65	1.03	0.98	1.05	1.03
SCA (Dhifallah et al., 2018)	0.84	0.73	0.73	0.65	1.06	0.92	1.02	1.01
netNorm	0.57	0.47	0.51	0.39	0.55	0.61	0.62	0.61

CBT discriminability. In addition to being well-centered, we demonstrate that netNorm produces well-representative templates in terms of preserving the distinctive traits for a given population. Therefore, we conducted a comparative study between ASD and NC populations (respectively LMCI and AD populations) for both hemispheres using the estimated CBTs. More specifically, we identified the top 15 discriminative ROIs distinguishing between two groups (ASD vs. NC and AD vs. LMCI) for each hemisphere using the absolute difference between the CBTs estimated using netNorm and each of the baseline methods (AA, SA, AS, SS and SCA). Then, we calculated the overlap between the most discriminative anatomical ROIs revealed using our method and those identified using MKL. **Table 4** displays the overlap in % between ranked most discriminative ROIs identified by (i) MKL and (ii) the absolute difference between the two estimated CBTs of the comparison methods, respectively. We note that netNorm, overall, achieved a significantly ($p < 0.05$) larger overlap in terms of top discriminative ROIs compared with those generated by comparison techniques across all datasets except for the right hemisphere in ASD/NC populations, where it fell behind SA

technique. Specifically, netNorm reached an overlap percentage of 86% for distinguishing AD from LMCI subjects using the left hemisphere and 80% for the right hemisphere.

In **Figure 8**, we visualize the top 15 discriminative ROIs selected using MKL and netNorm respectively. We represent each of the selected ROIs using its normalized score α depicting its discriminability power in distinguishing between different populations for all datasets using both hemispheres. We note that, the most discriminative ROIs selected by netNorm in distinguishing between LMCI and AD populations include the pericalcarine cortex (region 21) (Wee et al., 2013) and the entorhinal cortex (region 6) associated with a decreased volume in subjects with Alzheimer’s disease in comparison to those with mild cognitive impairment (Devanand et al., 2007) for the right hemisphere and the pericalcarine cortex (region 21) and the Rostral middle frontal gyrus (region 27) (Wee et al., 2013) for the left hemisphere, respectively.

Table 4. Matching rate in % between top discriminative ROIs identified by MKL method and the difference between connectional templates estimated for ASD/NC and AD/LMCI populations.

Datasets	AD/LMCI		ASD/NC	
	LH	RH	LH	RH
AA	66.67	73.34	53.54	53.54
AS	46.67	46.67	40.00	46.67
SA	73.34	73.34	53.34	73.34
SS	75.27	72.54	16.92	16.65
SCA	73.33	66.7	60	60
(Dhifallah et al.) netNorm	86.66	80.00	66.67	66.67

Thus, by applying netNorm to healthy and disordered populations, we show that the estimated CBTs reliably spot altered brain regions differentiating healthy and pathological groups. More importantly, **Table 5** displays the top 5 discriminative ROIs distinguishing between healthy and autistic subjects (ASD vs. NC populations) using netNorm for both RH and LH, which are

consistent with previous findings on atypical regions in autistic subjects in the literature. More specifically, we note that both the pericalcarine cortex and the entorhinal cortex are selected as the most discriminative ROIs determined by netNorm that differentiate between healthy and autistic subjects for both hemispheres. These regions are known to be related to ASD (Zielinski et al., 2014; Wegiel et al., 2010). In particular, the entorhinal cortex is highly correlated with hyperactivity, aggression and self-injurious behavior in autistic subjects.

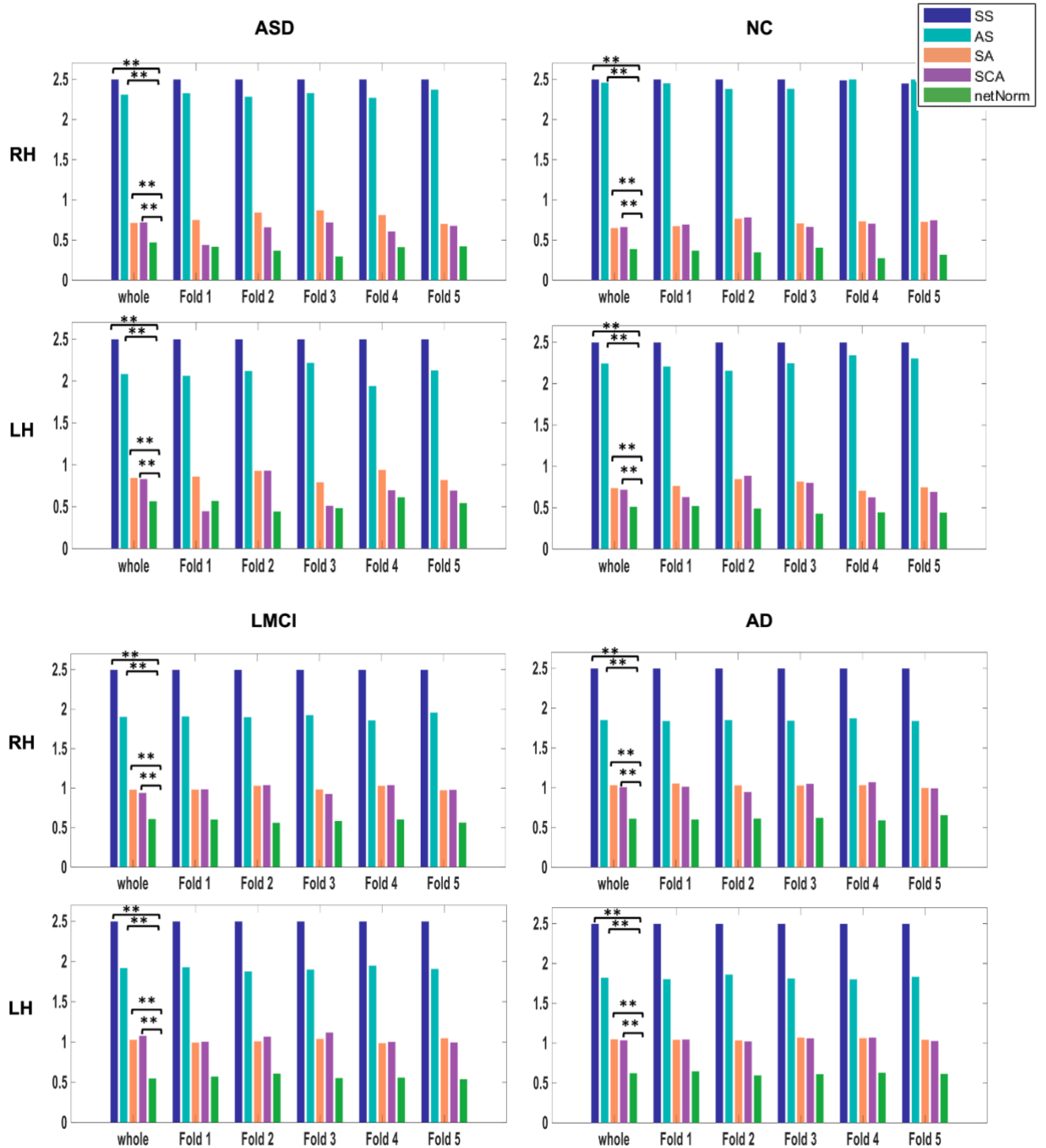
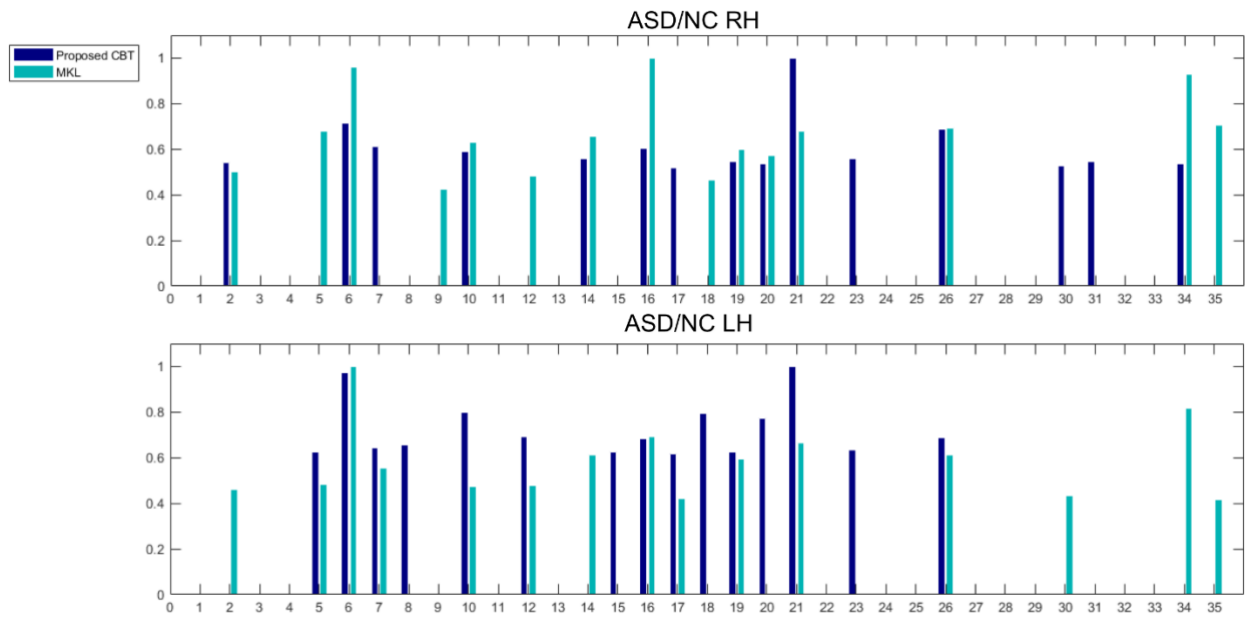


Fig. 7. Evaluation of netNorm performance. Average Frobenius distance between the estimated connectional brain template (CBT) and all views in the original space using netNorm and benchmark methods for the left and right cortical hemispheres in ASD, NC, LMCI and AD populations. In addition to SCA technique introduced in (Dhifallah et al., 2018), comparison methods apply linear averaging (A) or nonlinear similarity network fusion (S) techniques in the following two steps: (i) merging brain network views for each subject into a single network, and (ii) merging brain networks across all subjects. (**) for $p\text{-value} < 0.001$ using two-tailed paired t-test.



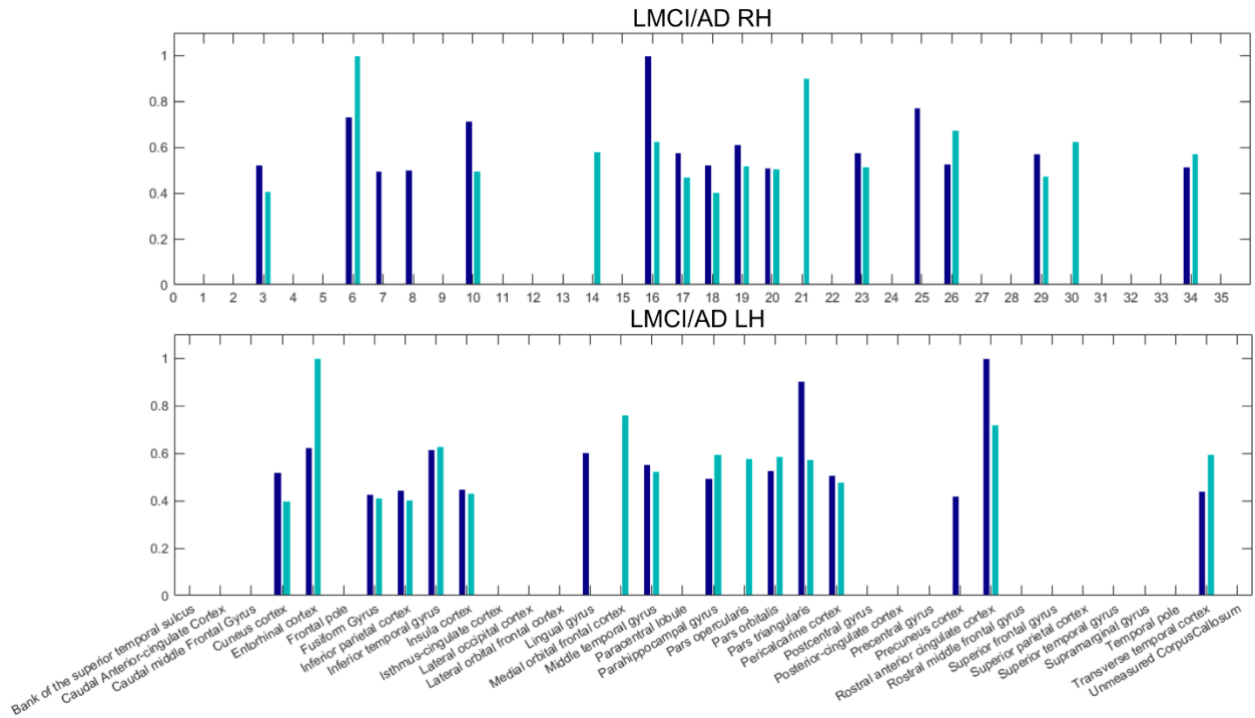





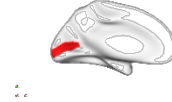

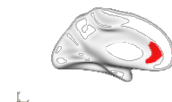
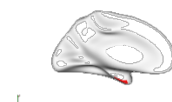
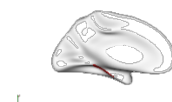


Fig. 8. Assessing the discriminability of the estimated population-specific connectional brain template by netNorm. We identify top 15 discriminative ROIs of LH using (i) multiple-kernel learning (MKL) and (ii) the template absolute difference between two brain populations for the right and left hemispheres (RH and LH).

Table 5. Top 5 discriminative regions of interest (ROIs) in the left and right hemispheres distinguishing between normal controls (NC) and autistic (ASD) subjects identified by computing the absolute difference between ASD and NC estimated CBTs built using netNorm.

Left Hemisphere	Top 5 discriminative ROIs	Behavioural effect in autism	ROI representation
	Pericalcarine cortex	Thicker cortex in autistic children in comparison to NC (Zielinski et al., 2014).	
	Entorhinal cortex	Hyperactivity, aggression and self-injurious behaviour (Wegiel et al., 2010).	
	Isthmus cingulate cortex	Impairment in social behavior (Doyle-Thomas et al., 2013).	

	Pars opercularis	Social communication problems (Yamasaki et al., 2010).	
	Pars triangularis	Language impairment (Fossé et al., 2004)	
Right Hemisphere	Pericalcarine cortex	Thicker cortex in autistic children in comparison to NC (Zielinski et al., 2014).	
	Entorhinal cortex	Hyperactivity, aggression and self-injurious behavior (Wegiel et al., 2010).	
	Rostral anterior cingulate cortex	Aggression (Wegiel et al., 2010).	
	Fusiform Gyrus	Difficulties in face perception and persons' recognition (Kooten et al., 2008; Waiter et al., 2004).	
	Parahippocampal gyrus	Abnormal social cognition function (Xiaoyan et al., 2008).	

5. Discussion

In this paper, we introduced netNorm, a novel framework for connectional brain template estimation that leverages complementary information offered by different brain views for a population of multi-view brain networks. We first built multi-view brain connections between different regions of the brain for a population of subjects, then we defined a cross-view feature vector between each pair of ROIs for each individual in the population. In order to investigate the inter-relationship between different subjects in the population at a local scale, we constructed a high-order graph for each pairwise connection capturing the dissimilarities between the cross-view feature vectors across all subjects. A selection process is then applied to construct a multi-view population representative tensor through selecting the most common

cross-view feature vectors among the population. The estimated CBT is then generated by fusing the different views of the estimated tensor. We aimed to use the produced connectional templates in order to identify potential biomarkers for neurodevelopmental (ASD) and neurodegenerative (AD) disorders.

CBT representativeness and centeredness. Our proposed method achieved the best performance in terms of centredness where the estimated CBT had the minimum mean distance to all network views in the population (**Figure 7, Table 3**). These results can be explained by the fact that while conventional methods (AA, AS, SA, SS) integrate the network views *equally* by merging them at a global scale, whereas netNorm learns how to fuse them at a local scale by first selecting for each local pairwise connection between two ROIs the most representative cross-view feature vector in the population. More specifically, through building a high-order graph that captures the dissimilarities between different feature vectors across all subjects, netNorm builds a population representative tensor including feature vectors having the minimum distance in the graph. Therefore, instead of equally combining feature vectors across the whole population (e.g. through average or SNF), netNorm only selects the most common subject-specific feature vectors. The obtained tensor is a mosaic representation of the whole population that occupies a centered location to all subjects in the group. Thus, through satisfying the centredness criteria of the population representative tensor, netNorm ensures the centredness of the estimated CBT.

CBT discriminability. Different studies have shown that the complementary information offered by different brain modalities play an important role in identifying potential biomarkers for neurological disorders (Apostolova et al., 2010; de Leon et al., 2007). Defining a unified representation of a population of multi-view brain networks represents a key step for comparative studies. A naive practice in defining a population’s template is by averaging the population’s different views. However, this may not be enough to effectively merge complementary information and preserve the population’s discriminative traits. In this paper, one important advantage of our proposed technique is its discriminative power in distinguishing between different populations as shown in **Table 4** and **Figure 8**. These results indicate the effectiveness of the proposed framework against *inter-subject variability* while enforcing the population’s common and distinct traits. This can be explained, first, by the fact that the estimated CBT occupies the minimum distance compared to all subjects in the population which results in minimizing the inter-individual variability. Second, through defining a selection

process that only takes into account the most common cross-view feature vectors across the whole population, netNorm builds a selective and reliable multi-view representation of the population before applying the final fusion process. Therefore, through constructing a high-order graph that captures the commonality aspect of each feature vector across subjects, netNorm explores the global architecture between subjects at the feature vector scale by exploring their inter-connections. In addition, through applying SNF for non-linear fusion of the representative views, netNorm explores the complementary information offered by different representative brain modalities. SNF fuses complementary data lying on different manifolds by an iterative process that adds strong connections between different networks to one another while discarding weak connections (Wang et al., 2014). Therefore, ensuring a more robust representation of a population's connectional characteristics and conserving its distinct traits. We believe that our proposed method will pave the way for more representative CBT estimation techniques, stimulating a deeper understanding of neurodegenerative and neurodevelopmental diseases using different data sources.

We display in **Table 5** the top 5 discriminative ROIs distinguishing between healthy and autistic subjects for the right and left hemispheres by computing the absolute difference between the estimated CBTs and pinning down regions with highest differences. We show that the pericalcarine cortex followed by the entorhinal cortex represent the most 2 discriminative ROIs for both hemispheres. We note that the human brain presents hemispheric asymmetries that occur by nature (Wada et al., 1975) or through the asymmetric influence of autism (Chiron et al., 1995; Herbert et al., 2004), which explains the asymmetry between the remaining discriminative regions for both hemispheres. We also note that our findings are consistent with previous studies where most of the identified ROIs obtained using netNorm are correlated with behavioral impairments in autistic subjects. Particularly, for the left hemisphere the isthmus cingulate cortex which is responsible for social behavior impairment (Doyle-Thomas et al., 2013), the pars opercularis affecting the social communication skills and the pars triangularis responsible for language impairment were identified as discriminative ROIs between ASD and NC groups. For the right hemisphere, however, we identified other discriminative regions including the rostral anterior cingulate cortex explaining the aggressive behavior in autistic subjects (Wegiel et al., 2010), the fusiform gyrus responsible for the difficulties in face perception and persons' recognition (Kooten et al., 2008; Waiter et al., 2004) and the parahippocampal gyrus affecting the social cognitive function for ASD subjects (Xiaoyan et al., 2008).

Limitations. Our work has a few limitations. First, we evaluated netNorm on morphological connectomic data using Desikan-Killiany brain atlas, yet our framework is a generic method that can be applied to different connectional modalities (e.g., functional and structural connectomes) and using different brain parcellation (Glasser et al., 2016). We note that, for a given population, the same parcellation template shall be consistently used across all network modalities and across all subjects. Second, we only tested netNorm on morphological brain networks capturing different attributes. For future work, we can consider combining different brain views derived from different imaging modalities (e.g., structural and morphological brain networks) in order to explore diverse and complementary information. Third, we used Euclidean distance as a dissimilarity metric to build a high-order graph between different cross-view feature vectors, which alternatively can be *learned* to better model the high dimensionality of feature vectors derived from multi-view networks. Forth, although we identified morphological ROIs biomarkers for ASD and AD diseases, we did not examine the connectional aspect between these regions. These unexplored directions can be further investigated in our future work.

6. Conclusion:

In this paper, we unprecedentedly propose netNorm framework for normalizing a population of multi-view brain networks by estimating a well-representative and centered connectional brain template using a selective fusion process. Specifically, we applied a selection strategy for building a multi-view population representative tensor based on a commonality criterion for cross-view feature vectors' selection among all subjects. Then we constructed the final template by non-linearly fusing the different representative views. The proposed method outperformed the baseline methods on four datasets composed of ASD, NC, AD, and LMCI subjects, respectively, in terms of (i) centredness and representativeness compared to all subjects and all views in the population and (ii) discriminability in preserving the population characteristics. In our future work, we will explore manifold learning techniques to enhance the non-linear fusion process. Also, we will evaluate our framework on other types of brain network views including positive and negative values (e.g. functional brain connectivity) on larger datasets.

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